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Exposure to parental depression in adolescence and proinflammatory phenotypes 20 years later

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ABSTRACT

Although the biological embedding model of adversity proposes that stressful experiences in childhood create a *durable* proinflammatory phenotype in immune cells, research to date has relied on study designs that limit our ability to make conclusions about whether the phenotype is long-lasting. The present study leverages an ongoing 20-year investigation of African American youth to test research questions about the extent to which stressors measured in childhood forecast a proinflammatory phenotype in adulthood, as indicated by exaggerated cytokine responses to bacterial stimuli, monocyte insensitivity to inhibitory signals from hydrocortisone, and low-grade inflammation. Parents reported on their depressive symptoms and unsupportive parenting tendencies across youths' adolescence. At age 31, youth participants (now adults) completed a fasting blood draw. Samples were incubated with lipopolysaccharide and doses of hydrocortisone to evaluate proinflammatory processes. Additionally, blood samples were tested for indicators of low-grade inflammation, including IL-6, IL-8, IL-10, and TNF-α, and soluble urokinase plasminogen activator receptor. Analyses revealed that parental depression across youths' adolescence prospectively predicted indicators of proinflammatory phenotypes at age 31. Follow-up analyses suggested that unsupportive parenting mediated these associations. These findings suggest that exposure to parental depression in adolescence leaves an imprint on inflammatory activity that can be observed 20 years later.

1. Introduction

Multiple theories focused on early adversity (Barker, 1995; Coe and Lubach, 2007; Gluckman et al., 2010; Gunnar & Quevedo, 2007; Miller & Chen, 2013; Miller et al., 2011; Weaver et al., 2004) propose that social and contextual experiences in childhood calibrate systems in the body in ways that have a lasting influence on adult physical health. For example, the biological embedding model focuses on changes to monocytes and macrophages, which are immune cells that are centrally involved in the inflammatory response. In response to stressful social and environmental conditions, these cells are thought to be programmed to have a proinflammatory phenotype, which manifests in relatively aggressive inflammatory responses to stimuli and lower monocyte sensitivity to the negative feedback signals that dampen the inflammatory response (e.g., anti-inflammatory signals from cortisol). If sustained, this phenotype may contribute to low-grade systemic inflammation, which is causally involved in the development and progression of age-related diseases, including heart disease, stroke, and metabolic disorders (Hotamisligil, 2006; Nathan & Ding, 2010).

To date, most attempts to document evidence of biological embedding of adversity have relied on (a) studies with relatively brief time windows between assessments of childhood stressors and inflammation (e.g., Ehrlich et al., 2021), (b) retrospective studies that capture adolescent participants' memories of early life experiences (e.g., Miller & Chen, 2010), or (c) studies where circulating inflammatory markers are collected to serve as proxy indicators of inflammatory activity (e.g., Liu et al., 2017; Milaniak & Jaffee, 2019; Plant et al., 2016). Each of these approaches has some limitations, however. First, with regard to

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the short intervals between measurement of stressors and inflammation indices, one question left unanswered is whether such evidence of inflammation is chronic or transitory. For it to be involved in the progression of age-related diseases, inflammation would need to be sustained over a period of years or even decades, where it would then have sufficient time to act on relevant tissues and disrupt processes in ways that contribute to chronic disease (e.g., formation of fatty streaks in the development of atherosclerosis; Tedgui & Mallat, 2006; development of insulin resistance; Shoelson et al., 2006). Retrospective studies have a different limitation, in that adults' reports of childhood adversity may be biased by a variety of factors, such as personality, mental health, and measurement error (e.g., Hardt & Rutter, 2004; Reuben et al., 2016). As such, these reports of childhood experiences may reflect some combination of past and current experiences, which obscures definitive tests of whether *childhood* adversities predict proinflammatory phenotypes in adulthood. Finally, studies that rely on circulating markers of inflammation (such as cytokines or C-reactive protein [CRP]) do not necessarily provide key information about the possible *mechanisms* linking adversity to health because these signaling molecules are released into the bloodstream for a variety of reasons, some of which have little to do with infection or tissue damage (Cohen and Cohen, 1996; Hunter & Jones, 2015; Moldoveanu et al., 2001).

As an addition to the common approach of measuring circulating markers of low-grade inflammation, in the present study we use a stimulated cell culture paradigm that allows us to create standardized conditions of microbial threats to evaluate how people's immune cells actually respond when presented with a challenge. Using this same method, we can also capture information about monocytes' sensitivity to anti-inflammatory signals, such as when cells are cultured with both bacterial products and cortisol (which should inhibit the inflammatory response). Together, these ex vivo methods provide direct information about people's proinflammatory phenotypes by capturing both the "gas" and "brakes" of the innate inflammatory response (Ehrlich et al., 2016). A handful of studies have used this stimulated cell culture method to explore questions about how adversity in childhood and adolescence is linked to proinflammatory outcomes in adolescence (Ehrlich et al., 2016) and across the lifespan (Chiang et al., 2022; Lam et al., 2022). In each of these studies, analyses were performed using cross-sectional or short-term longitudinal studies. Given the time, expense, and resources involved in this work, the field's reliance on cross-sectional and short-term longitudinal studies is a sensible decision, but ultimately it leaves open questions about whether experiences measured in childhood forecast proinflammatory phenotypes decades later. In the present study, we also include a composite measure of low-grade inflammation, which allows our findings to be integrated with the broader literature linking childhood stressors to adult inflammation (e.g., Allen et al., 2018; Danese et al., 2009). Our composite includes IL-6, IL-8, IL-10, and TNF-α, and soluble urokinase plasminogen activator receptor (suPAR), which are markers that reflect ongoing inflammation and are prognostic of chronic disease morbidity (Libby et al., 2009; Rasmussen et al., 2021; Ridker, 2007).

Long-term prospective studies provide a solution to some of the study limitations described above. Until recently, however, few ongoing studies were available that included assessment of childhood stressors—*measured in childhood*—and subsequent measurement of proinflammatory activity in adulthood. The present study leverages a longitudinal study of African Americans in the rural South, who have been participating in the study for two decades, starting when youth were approximately 11 years old (Brody et al., 2004). Across their child's adolescence, parents reported on various challenges, including their depressive symptoms, socioeconomic disadvantage, and unsupportive parenting tactics.

We focused specifically on whether exposure to parental depression across adolescence was predictive of youths' inflammatory outcomes in adulthood for three reasons. First, parental depression is a relatively common phenomenon, affecting an estimated 7.5 million parents in the United States annually (England & Sim, 2009; Ertel et al., 2011). Its high prevalence rate means that around 15 million children are exposed to this stressor each year. Second, there is evidence that parents' depression is associated with other health-relevant outcomes for their offspring, including indicators of metabolic dysregulation (Ehrlich et al., 2019; Mannie et al., 2013) and obesity (Gundersen et al., 2008). Finally, relative to other prevalent stressors that are not easily ameliorated at the family level (e.g., poverty), parental depression is a modifiable target for intervention (e.g., Beardslee et al., 2007; Solantaus et al., 2009). Efforts to address parents' mental health can lead to psychosocial benefits for children (Giannakopoulos et al., 2021) and may similarly have long-term physical health benefits.

Parental depression may contribute to inflammatory outcomes in their children due to disruptions in parents' abilities to provide supportive and nurturing caregiving (Dix & Moed, 2019). Relative to parents without depression, depressed parents are more likely to employ harsh or insensitive caregiving tactics (Dix & Meunier, 2009), and children, in turn, perceive their caregivers as an unreliable source of comfort (Woodhouse et al., 2010). The lack of supportive caregiving is thought to contribute to children's physiological stress response activity and can undermine their developing emotion regulation capacities (Luecken & Lemery, 2004; Morris et al., 2017). By adolescence, youth have developed strategies for regulating their own emotions, but parents continue to support adolescents' emotion regulation through their parenting practices and the broader family emotional climate (Felton et al., 2022; Morris et al., 2017; Yap et al., 2007). Collectively, these parental behaviors are thought to influence children's psychosocial development and their abilities to tolerate distress, all of which may foster increased inflammatory activity in adulthood.

In the present study, we tested the hypothesis that parental depression measured across adolescence would be prospectively associated with youths' proinflammatory phenotypes in adulthood, as indexed by monocyte cytokine responses to bacterial stimulation, sensitivity to glucocorticoid inhibition, and biomarkers of low-grade inflammation. Adolescence is widely viewed as a second critical period of development (Blakemore, 2008), and experiences during this period are thought to have an outsized impact on long-term development. Additionally, this period is a time of further maturation and development of the immune system (Brenhouse and Schwarz, 2016), making this stage of development an especially sensitive period for long-term programming of monocyte functions in ways that may become durable over time. We also tested whether unsupportive parenting practices mediated the associations between parental depression and markers of the proinflammatory phenotype. We hypothesized that exposure to parental depression would be positively associated with unsupportive parenting, which in turn would be prospectively associated with low-grade inflammation, as well as monocyte cytokine responses to bacterial stimulation and sensitivity to glucocorticoid. Finally, we considered a series of exploratory models, including tests to examine whether the impact of parental depression on inflammatory outcomes was moderated by unsupportive parenting, socioeconomic disadvantage, or child sex. Additionally, given evidence that parental depression is linked to children's depression (Beardslee et al., 2011), and depression has been linked to inflammation (e.g., Dantzer, 2012; Irwin & Miller, 2007), we tested an alternative model wherein youths' depression mediated the proposed association between parental depression and youth inflammatory outcomes.

2. Materials and methods

2.1. Participants

Data for the study come from the Strong African American Families Healthy Adult Project (SHAPE; Brody et al., 2013). Starting in 2001, SHAPE enrolled 667 Black children in fifth grade (mean age = 11.2 years, $SD = 0.3$) along with their primary caregivers. Families resided in

rural counties in Georgia, where poverty rates are among the highest in the United States. Primary caregivers (90 % mothers) had a median household income of $1612 per month; 42.3 % lived below federal poverty thresholds. In 2009–2010, when participants were 19 years old, a subsample of 500 participants were randomly selected to participate in a substudy of stress hormones and blood pressure. In 2021–2022, when the participants were aged 31 years old, we reassessed the cohort and obtained blood draws from 346 participants, from which indicators of a pro-inflammatory phenotype and circulating inflammatory biomarkers were assessed. The analytic sample in this study consisted of 332 individuals selected from this subsample. Fourteen participants were excluded from analysis because of technical problems with blood collection or processing. Compared with the original study cohort, the analytic sample had a higher percentage of female participants (64.5 % vs. 52.8 %) and experienced more years living in poverty (*M*s = 2.39 vs. 2.16); the samples were similar on the other study variables. The University of Georgia's Institutional Review Board approved the protocol, and written consent was obtained from participants and their caregivers at all assessments.

2.2. Procedures

All data were collected in participants' homes using a standardized protocol. African American field researchers visited families' homes to administer computer-based interviews, allowing respondents to answer sensitive questions privately. When participants were aged 31 (on average), a phlebotomist went to each participant's home in the morning to draw a fasting blood sample. To minimize circadian variation, venipuncture was performed between 8:00 am and 10:00 am. Participants fasted for 8 h beforehand to minimize dietary influences. Participants were instructed to contact the research team and reschedule the home visit if they were ill.

2.3. Measures

2.3.1. Parental depression

When participants were 11, 12, and 13 years of age, parents reported their past week depressive symptoms on the Center for Epidemiologic Studies Depression scale (CES–D; Radloff, 1977), which is widely used with community samples. Parents rated 20 symptoms on the following scale: 0 (*rarely or none of the time*), 1 (*some or little of the time*), 2 (*occasionally or a moderate amount of time*), or 3 (*most or all of the time*). Alphas were ranged from 0.85 to 0.87 across three assessment waves. Responses were summed across items and were averaged across three assessments to form the parental depression scores.

2.3.2. Unsupportive parenting

We created an index of unsupportive parenting, which was assessed at participants' ages of 16, 17, and 18 years, and was derived from parent reports of parent–child conflict and emotional support. Parent-child conflict was measured using an adaptation of the Ineffective Arguing Inventory (Kurdek, 1994). On a scale ranging from 1 (*disagree strongly*) to 5 (*agree strongly*), parents rated statements about the conflicts they had with their children, such as "You and your child's arguments are left hanging and unsettled" and "You and your child go for days being mad at each other." Cronbach's alphas for this scale ranged from 0.75 to 0.78. Responses were summed across items and were averaged across three assessments to form the parent–child conflict scores. The 4-item Emotional Support subscale from the Carver Support Scale (Carver et al., 1989) was administered at ages 16–18. On a scale ranging from 1 (*not at all true*) to 5 (*very true*), parents responded to items such as, "My child discusses his/her feelings with me" and "My child gets sympathy and understanding from me." Cronbach's alphas for this scale ranged from 0.80 to 0.81. Responses were summed across items and were averaged across three assessments to form the parental emotional support scores. Scores for parental emotional support and parent–child conflict were highly correlated ($r = -0.57$, $p < .001$). They were standardized and the parental emotional support scores were subtracted from the parent–child conflict scores. High values indicated high conflict and low levels of emotional support.

2.3.3. Proinflammatory phenotype

To quantify features of the proinflammatory phenotype, we used a portable cell culture protocol developed for field settings (McDade et al., 2021) when participants were age 31. In this protocol, immune cells are incubated *ex vivo* with a bacterial product (lipopolysaccharide [LPS]), and we examine the production of proinflammatory cytokines including interleukin (IL)-6, IL-1β, and tumor necrosis factor-alpha (TNF-α). Additionally, hydrocortisone is added to separate cultures with LPS to examine how sensitive participants' immune cells are to the anti-inflammatory properties of glucocorticoids.

Phlebotomists drew 6-ml of fasting antecubital blood into a Sodium Heparin Vacutainer (Becton-Dickinson). Then, 250 μl of blood was dispensed into microfuge tubes containing LPS (diluted in R10 media to an in-well concentration of 50 ng/ml) and hydrocortisone (diluted in R10 media to in-well concentrations of either 10^{-6}, 10^{-5}, or 0 nM). (Budget constraints restricted the number of hydrocortisone concentrations we could include in this analysis, but these doses have been shown to produce maximum variability in glucocorticoid sensitivity [McDade et al., 2021].) A negative control was also prepared to measure nonspecific cytokine production, where 250 μl of blood was added to a microfuge tube with 97 μl of R10. In all conditions, the final in-well dilution of blood was 72 % v/v. The samples were incubated in a portable device for 6 h at 37 °C (Embryonentransp Model 19180; Minitube GmbH), after which supernatants were harvested by centrifugation and frozen at −80 °C. At the end of the study, samples were thawed, diluted 42-fold, and tested for IL-6, IL-1β, and TNF-α with an automated microfluidic platform (Simple Plex, Protein Simple). Each cytokine was measured in triplicate, and the intra-assay coefficients of variation (CV) were 2.41 % for IL-6, 3.67 % for IL-1β, and 1.91 % for TNF-α. The inter-assay CV's were 6.24 % for IL-6, 8.23 % for IL-1β, and 5.37 % for TNF-α.

These assays yielded a large volume of data. With 3 cytokines measured in 4 conditions, 12 outcome variables were produced. To alleviate concerns about false discovery, we decided a priori to conduct primary analyses on two composite endpoints. Before the composites were calculated, raw cytokines values were natural log transformed to correct for skewness in their distribution. To adjust for nonspecific cytokine production, we used regression to residualize values from the negative control well - with R10 media alone - from cytokines produced in the LPS condition. 14 participants had excessive cytokine production in the negative control well, defined as more than 2 SD above the sample mean. Because these values could reflect contamination, incubator failures, or other technical problems, we excluded these participants from analysis.

The first composite we created was a *stimulated cytokine production composite*, formed by averaging z-scored values of the three cytokines, which were strongly inter-correlated (Spearman *r*'s from 69 to 0.78). The composite was internally consistent (Cronbach's $\alpha = 0.85$) and scored so that higher values represent larger cytokine responses to LPS. The second was a *monocyte sensitivity to glucocorticoid inhibition composite*. It was formed by estimating participant-specific sensitivity slopes for each cytokine (Chiang et al., 2019; Lam et al., 2022). The z-scored values of the cytokine slopes were then averaged, given the pattern of strong intercorrelation among them (Spearman *r*'s from 0.66 to 0.74). Again, the composite was internally consistent ($\alpha = 0.91$) and scored so that higher values represent greater monocyte sensitivity to the anti-inflammatory properties of glucocorticoids.

2.3.4. Low-grade inflammation

At age 31, blood was drawn into Serum Separator tubes (Becton, Dickinson and Company, Franklin Lakes, NJ, USA). Specimens were centrifuged on site at 1500 × g for 20 min. The serum was harvested,

divided into aliquots, and immediately frozen on dry ice. Upon arrival at the lab, it was placed in storage at –80° C until the end of the project. CRP, circulating cytokines IL-6, IL-8, IL-10, and TNF-α, and suPAR were assayed in batch. CRP was measured in triplicate by simplex immunoassay on a microfluidic platform (Simple Plex; Protein Simple). The intra-assay and inter-assay coefficients of variation were 2.67 % and 11.03 %, respectively. The cytokines were assayed in in triplicate via four-plex immunoassay on a microfluidic platform (Simple Plex; Protein Simple). Across runs, the average intra-assay coefficients of variation were 3.75 % (IL-6), 2.45 % (IL-8), 5.78 % (IL-10), and 2.21 % (TNF-α). The inter-assay coefficients of variation were 4.95 % (IL-6), 5.04 % (IL-8), 10.99 % (IL-10), and 4.06 % (TNF-α). Finally, suPAR was assessed in triplicate by three-plex enzyme-linked immunosorbent assay (ELISA) on a microfluidic platform (Simple Plex; Protein Simple). The intra-assay and inter-assay coefficients of variation were 2.95 % and 4.73 %, respectively. When a sample value was above the highest standard, we diluted and re-assayed. All of the inflammatory biomarkers (CRP, IL-6, IL-8, IL-10, TNF-α, and suPAR) were skewed and/or kurtotic, so we normalized their distributions with log-10 transformations. The logged values of CRP, IL-6, IL-8, IL-10, TNF-α, and suPAR were then standardized and summed to form a composite score of low-grade inflammation.

2.3.5. Covariates

Sex was dummy coded; male participants were coded 1 and female participants were coded 0. The SHAPE cohort was initially recruited for a randomized controlled trial of a family-oriented intervention to prevent youth behavior problems and substance abuse. Participation in the intervention was not associated with any of the study outcomes; nevertheless, to minimize any residual confounding, we included a dichotomous covariate reflecting intervention condition (treatment vs. control) in all models. When participants were 11, 12, 13, 16, 17, and 18 years of age, parents provided data on their families' income-to-needs ratios based on family size; these data were used to compute household poverty. We created a sum score based on participants' poverty status at each of the six time points, which reflected the number of years participants lived below federal poverty standards. The majority of parents who completed the depression and parenting measures were mothers (89.9 %), with the remaining caregivers being grandmothers (4.6 %), fathers (3.6 %), or others (e.g., aunts; 1.9 %). We included a dichotomous covariate reflecting the guardian's status (mother = 1 and all others = 0) in all models. Finally, we measured participants' height and weight at age 31, and BMI is included in all models to account for obesity-related elevations in inflammatory markers (O'Connor et al., 2009).

2.4. Data analytic approach

We calculated Pearson's and Spearman's correlation coefficients to examine the associations of stimulated cytokine production, monocyte sensitivity to anti-inflammatory signaling, and low-grade inflammation with parental depression and unsupportive parenting. Multiple linear regression models were executed to test the study hypotheses. The first set of models was designed to determine whether parental depression across ages 11–13 was associated with stimulated cytokine production, monocyte sensitivity to anti-inflammatory signaling, and low-grade inflammation at age 31. The second set of models was designed to determine whether unsupportive parenting at ages 16–18 mediated the association between parental depression and our inflammatory outcomes. Mediation was tested using regression-based mediation effect analyses procedures (Hayes, 2018). To do this, regression coefficients were calculated for the associations of parental depression with unsupportive parenting (path A), and for the associations of unsupportive parenting with stimulated cytokine production, monocyte sensitivity to anti-inflammatory signaling, and low-grade inflammation (path Bs). The indirect effects in which unsupportive parenting serves as the mediator connecting parental depression to stimulated cytokine production, monocyte sensitivity to anti-inflammatory signaling, and low-grade inflammation were quantified as the product of the two regression coefficients (A × B). In addition, nonparametric bootstrapping was used to obtain the bias-corrected and accelerated confidence intervals (BCA) of parameter estimates for significance testing (Preacher et al., 2007). The parameter estimate was calculated 5000 times using random sampling with replacement to build a sampling distribution. In all models, sex, intervention status, family poverty across ages 11–18, and BMI at age 31 were included as covariates. All analyses were conducted using Mplus 8.9 (Muthén & Muthén, 1998-2018).

3. Results

Bivariate correlations and descriptive statistics for the study variables are presented in Table 1.

3.1. Parental depression across ages 11–13 and inflammatory outcomes at age 31

Our initial analysis was designed to test whether parental depression during pre-adolescence was associated with stimulated cytokine production, monocyte sensitivity to anti-inflammatory signaling, and low-grade inflammation during young adulthood. The results of the regression models (see Table 2) revealed that parental depression across ages 11–13 was positively associated with stimulated cytokine production (b = 0.007, 95 % CI [0.001, 0.013], β = 0.116, p =.022) and was negatively associated with monocyte sensitivity to hydrocortisone's anti-inflammatory properties (b = -0.001, 95 % CI [-0.002, -0.0001], β = -0.110, p =.048) at age 31. Parental depression at ages 11–13 was marginally associated with low-grade inflammation at age 31 (b = 0.042, 95 % CI [-0.005, 0.090], β = 0.087, p =.079).

3.2. Unsupportive parenting at ages 16–18 as a mediator

The second set of regression models evaluated whether unsupportive parenting across ages 16–18 mediated the association between parental depression during pre-adolescence and inflammatory outcomes during adulthood. (Although the association between parental depression and low-grade inflammation was not significant, main effects are no longer considered to be a requirement for testing mediation; see O'Rourke & MacKinnon, 2018). The results (see Tables 3 and 4 and Fig. 1) revealed that unsupportive parenting across ages 16–18 mediated the association between parental depression across ages 11–13 and stimulated cytokine production, monocyte sensitivity to anti-inflammatory signaling, and low-grade inflammation at age 31. Higher levels of parental depression at ages 11–13 was associated with higher levels of unsupportive parenting at ages 16–18 (b = 0.082, 95 % CI [0.054, 0.110], β = 0.328, p <.001), which in turn was associated with higher stimulated cytokine production (b = 0.029, 95 % CI [0.002, 0.055], β = 0.119, p =.032), lower monocyte sensitivity to anti-inflammatory signaling (b = -0.007, 95 % CI [-0.012, -0.003], β = -0.169, p =.002), and higher levels of low-grade inflammation (b = 0.323, 95 % CI [0.115, 0.531], β = 0.166, p =.002) at age 31. Multiplying these coefficients yielded an indirect mediated effect of 0.002 (95 % bootstrapped CI of [0.0001, 0.005], p =.046) for stimulated cytokine production, an indirect mediated effect of -0.001 (95 % bootstrapped CI of [-0.001, -0.0001], p =.007) for monocyte sensitivity to anti-inflammatory signaling, and an indirect mediated effect of 0.027 (95 % bootstrapped CI of [0.007, 0.046], p =.009) for low-grade inflammation.

3.3. Exploratory analyses

We conducted a number of additional analyses to test exploratory questions. First, we tested whether parental depression and unsupportive parenting would interactively predict the inflammatory outcomes.

Table 1
Correlations and Descriptive Statistics among Study Variables.

Variable	Mean (*SD*) or %	Correlations 1	2	3	4	5	6	7	8	9
1. Sex, male	35.5 %	—								
2. Intervention	59.0 %	-0.008	—							
3. Guardian's status, mother	89.9 %	-0.038	0.089	—						
4. Family poverty (ages 11–18)	2.39 (1.89)	-0.038	0.015	0.047	—					
5. Parental depression (ages 11–13)	10.74 (7.07)	0.001	0.091	0.153**	0.226***	—				
6. Unsupportive parenting (ages 16–18)	0 (1.77)	0.120*	-0.056	-0.055	0.055	0.310***	—			
7. BMI (age 31)	33.57 (10.21)	-0.246***	-0.026	0.057	0.094	0.032	0.013	—		
8. Stimulated cytokine production (age 31)	0 (0.43)	0.211***	-0.048	-0.070	0.087	0.120*	0.180**	0.019	—	
9. Sensitivity to anti-inflammatory signaling (age 31)	0.73 (0.08)	-0.050	-0.049	-0.043	-0.013	-0.114*	-0.181***	-0.019	-0.169**	—
10. Low-grade inflammation (age 31)	−0.01 (3.45)	-0.177**	0.002	-0.073	0.068	0.087	0.177**	0.369***	0.065	-0.077

Pearson correlations were presented for continuous variables; Spearman's correlations were presented for dichotomous variables.
SD: standard deviation; BMI: body mass index.
$N = 332$; *p <.05. **p <.01. ***p <.001.

Table 2
Parental Depression with Stimulated Cytokine Production, Sensitivity to Anti-inflammatory Signaling, and Low-grade Inflammation.

Predictors	Stimulated Cytokine Production (age 31)			Sensitivity to Anti-inflammatory Signaling (age 31)			Low-grade Inflammation (age 31)		
	b	[95 % CI]	β	*b*	[95 % CI]	β	*b*	[95 % CI]	β
1. Sex, male	0.189***	[0.095, 0.282]	0.211	-0.006	[-0.023, 0.012]	-0.035	-0.438	[-1.181, 0.305]	-0.061
2. Intervention	-0.041	[-0.131, 0.050]	-0.047	-0.006	[-0.023, 0.011]	-0.037	0.168	[-0.566, 0.902]	0.024
3. Guardian's status, mother	-0.144	[-0.309, 0.021]	-0.095	-0.009	[-0.035, 0.017]	-0.034	−1.680*	[-3.118, -0.241]	-0.138
4. Family poverty (ages 11–18)	0.015	[-0.009, 0.040]	0.067	0.001	[-0.004, 0.005]	0.015	0.034	[-0.132, 0.201]	0.019
5. BMI (age 31)	0.003	[-0.002, 0.007]	0.064	-0.000	[-0.001, 0.001]	-0.024	0.121***	[0.085, 0.156]	0.358
6. Parental depression (ages 11–13)	0.007*	[0.001, 0.013]	0.116	-0.001*	[-0.002, -0.0001]	-0.110	0.042	[-0.005, 0.090]	0.087

$N = 332$; b = unstandardized regression coefficient; CI = confidence interval; β = standardized regression coefficient;
BMI: body mass index. Family poverty at ages 11–18, sex, intervention status, guardian's status, and BMI at age 31 were covariates.
*p <.05. **p <.01. ***p <.001.

Table 3
Parental Depression with Unsupportive Parenting.

Predictors	Unsupportive Parenting (ages 16–18)		
	b	[95 % CI]	β
1. Sex, male	0.442*	[0.061, 0.822]	0.120
2. Intervention	-0.278	[-0.638, 0.081]	-0.078
3. Guardian's status, mother	-0.579	[-1.265, 0.106]	-0.093
4. Family poverty (ages 11–18)	-0.009	[-0.103, 0.085]	-0.009
5. Parental depression (ages 11–13)	0.082***	[0.054, 0.110]	0.328

$N = 332$; b = unstandardized regression coefficient; CI = confidence interval; β = standardized regression coefficient; Family poverty at ages 11–18, sex, guardian's status, and intervention status were covariates.
*p <.05. **p <.01. ***p <.001.

No significant interactive effects were identified. Second, we tested whether participant sex and family poverty moderated any of the reported findings; no moderation effects emerged. Our final exploratory analysis considered whether youth depression measured between ages 19–27 mediated the associations between parental depression and the inflammatory outcomes. Parental depression at ages 11–13 was not associated with youth depression between ages 19–27 (b = 0.081, p =.124; 95 % CI [-0.022, 0.184]), and youths' depression was not linked to any of the inflammatory outcomes at age 31 (all $ps > 0.10$).

4. Discussion

Although hundreds of studies have investigated the association between childhood adversity and inflammation (Chiang et al., 2022), this study is the first to explore how experiences *measured in childhood and adolescence* prospectively predict indicators of the proinflammatory

Table 4
Parental Depression and Unsupportive Parenting with Stimulated Cytokine Production, Sensitivity to Anti-inflammatory Signaling, and Low-grade Inflammation.

Predictors	Stimulated Cytokine Production (age 31)			Sensitivity to Anti-inflammatory Signaling (age 31)			Low-grade Inflammation (age 31)		
	b	[95 % CI]	β	*b*	[95 % CI]	β	*b*	[95 % CI]	β
1. Sex, male	0.175***	[0.080, 0.269]	0.196	-0.002	[-0.019, 0.015]	-0.014	-0.592	[-1.336, 0.152]	-0.082
2. Intervention	-0.033	[-0.123, 0.058]	-0.038	-0.008	[-0.025, 0.009]	-0.050	0.258	[-0.462, 0.977]	0.037
3. Family poverty (ages 11–18)	0.016	[-0.009, 0.040]	0.069	0.001	[-0.004, 0.005]	0.012	0.038	[-0.124, 0.201]	0.021
4. guardian's status, mother	-0.127	[-0.291, 0.037]	-0.084	-0.014	[-0.040, 0.012]	-0.050	−1.489*	[-2.848, -0.130]	-0.122
5. BMI (age 31)	0.002	[-0.002, 0.007]	0.059	-0.000	[-0.001, 0.001]	-0.017	0.119***	[0.084, 0.153]	0.352
6. Parental depression (ages 11–13)	0.005	[-0.002, 0.011]	0.077	-0.001	[-0.002, 0.001]	-0.054	0.016	[-0.033, 0.065]	0.033
7. Unsupportive parenting (ages 16–18)	0.029*	[0.002, 0.055]	0.119	-0.007**	[-0.012, -0.003]	-0.169	0.323**	[0.115, 0.531]	0.166

$N = 332$; b = unstandardized regression coefficient; CI = confidence interval; β = standardized regression coefficient;
BMI: body mass index. Family poverty at ages 11–18, sex, intervention status, guardian's status, and BMI at age 31 were covariates.
*p <.05. **p <.01. ***p <.001.

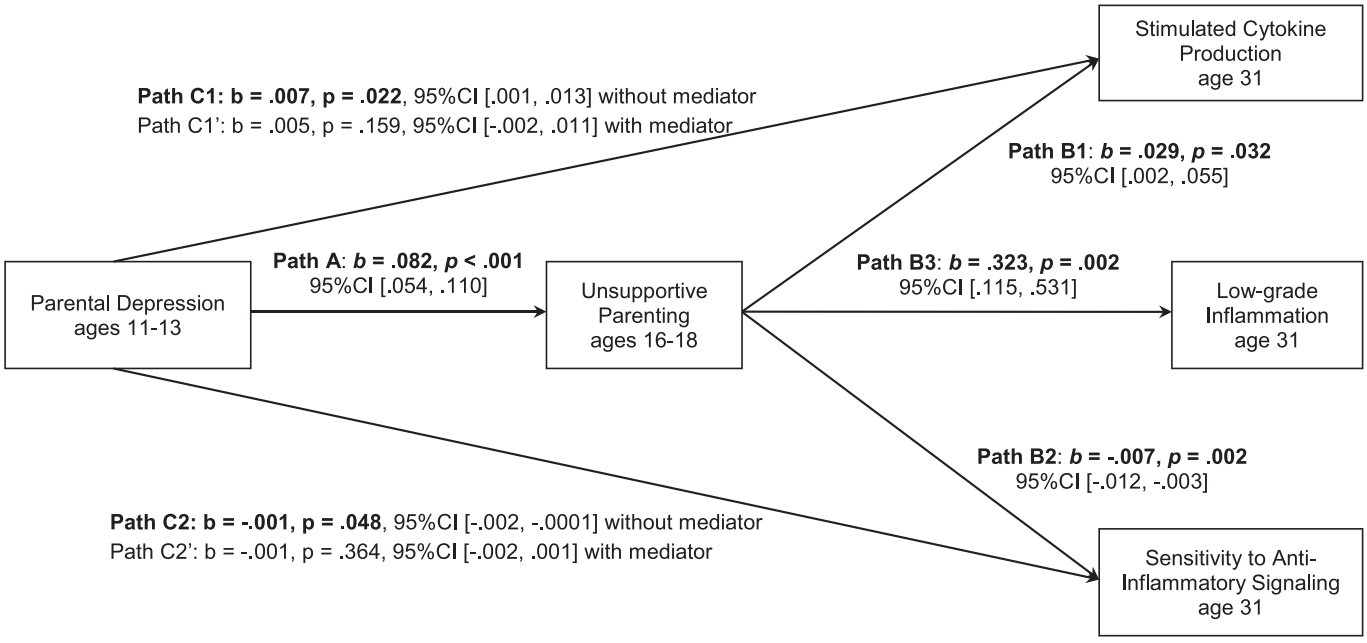

Fig. 1. Unsupportive parenting as the mediator of the relations between parental depression at ages 11–13 and stimulated cytokine production, sensitivity to anti-inflammatory signaling, and low-grade inflammation at age 31. Family poverty at ages 11–18, sex, intervention status, guardian's status, and BMI at age 31 were controlled (not shown). Unstandardized coefficients (b) with 95 % confident intervals (CI) are presented. N = 332.

phenotype decades later. Further, analyses suggested that this pathway was mediated by unsupportive parenting in adolescence. Although moderate conflict between parents and adolescents is normative (Holmbeck, 1996; Steinberg, 2001), our model suggests that destructive arguing, coupled with a lack of emotional support, forecasts elevated inflammatory markers over a decade later in adulthood. These findings add to the growing evidence suggesting that adverse experiences in childhood may become biologically embedded in ways that contribute to proinflammatory activity later in life. Moreover, these findings are consistent with the notion that adolescence is a sensitive period in development when experiences—particularly experiences in youths' social environments—may have an outsized impact on later development (Blakemore and Mills, 2014).

To date, this study has the largest time lag between assessments of childhood adversity and inflammatory outcomes, with approximately 20 years between the first assessment of parental depression and inflammatory outcomes in adulthood. One question that remains is whether similar patterns would have emerged had we measured proinflammatory activity in childhood or earlier in adulthood, or if the observed effects only emerge over time after the accumulation of stress exposures reaches a tipping point. Indeed, some evidence suggests that the magnitude of effects of early adversity on inflammatory outcomes increases across the lifespan (Chiang et al., 2022), so it is possible that the sequelae associated with parental depression may not have been observed in childhood. Another question these findings raise is whether the elevated inflammatory activity persists across adulthood and subsequently predicts elevated risk for chronic diseases, such as diabetes or cardiovascular disease. By mapping out these trajectories across the lifecourse, we can begin to address important questions about the cascading effects of childhood adversity on adult physical health.

Collectively, these findings provide evidence for the proposition that early social adversity programs biological systems in a way that persists for decades. Strengths of the study include the prospective design, with high rates of retention 20 years later, the novel in-field cell stimulation protocol, and the focus on African American families living in the rural South. At the same time, several study limitations will be important to address in future research. First, our study began when youth were 11 years old, and experiences in infancy and early childhood were not captured in our study design. Additional research that can leverage prospective birth cohort studies and multigenerational studies will help identify whether there are critical periods in development when exposure to stressful life experiences may shape health. Second, measures of parental depression and unsupportive parenting relied on parents' reports, and it is possible that parents' depression may have contributed to biased perceptions of their own parenting quality. For example, parental depression has been associated with reporting more negative parenting, relative to adolescents' reports (Ehrlich et al., 2014). Future studies could include behavioral observations of parenting, which may provide more context about *why* unsupportive parenting forecasts the inflammatory profiles observed over a decade later. For example, do youth who experience unsupportive parenting in adolescence turn to unhealthy foods for to alleviate their distress? Another likely possibility is that, when youth have not been able to rely on caregivers to meet their emotional needs, they may continue to experience stressors that contribute to wear and tear on biological systems (Ehrlich et al., 2016). Another study limitation is the lack of baseline assessment of inflammatory outcomes. Future longitudinal projects that incorporate repeated measurement of psychosocial risk factors and inflammatory outcomes will be better positioned to evaluate questions about how changes in risk exposure predict manifestations of the proinflammatory phenotype over time. Finally, this study cannot rule out other possible confounds, such as genetic factors or medication use during pregnancy that may shape both depression and inflammation across generations.

4.1. Conclusions

In summary, our findings respond to calls to use long-term prospective studies to test hypotheses about the biological embedding model (e.g., Ehrlich et al., 2016). These findings suggest that exposure to parental depression across adolescence predicts two key indicators of a proinflammatory phenotype at age 31. To the extent that this phenotype confers future risk for clinically relevant health problems, efforts to identify factors that might mitigate the effects associated with exposure to parental depression will be especially important.

CRediT authorship contribution statement

Katherine B. Ehrlich: Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing, Investigation, Project administration, Resources, Supervision. **Manuela L. Celia-Sanchez:** Project administration, Writing – review & editing, Investigation, Resources. **Tianyi Yu:** Conceptualization, Formal analysis, Funding acquisition, Visualization, Writing – original draft, Writing – review & editing, Software. **Nia Heard-Garris:** Conceptualization, Writing – review & editing. **Edith Chen:** Conceptualization, Funding acquisition, Writing – review & editing. **Gregory E. Miller:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing. **Gene H. Brody:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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